IN THE MATTER of European Patent Application No. 95943722.9

DECLARATION OF WILLIAM W. STORMS, M.D.

I, WILLIAM W. STORMS, do solemnly and sincerely declare that:

I. BACKGROUND

1. I am Clinical Professor of Medicine at the University of Colorado Health Sciences Center, Denver, Colorado, U.S.A., and am a practicing allergist. Since 1997, I have been a member of the Sports Medicine Committee of the U.S. Olympic Committee. My *curriculum vitae* is attached hereto as Exhibit A.

2. I received a Bachelor of Arts degree from Northwestern University in 1964 and a Medical Doctor degree from the University of Wisconsin Medical School in 1968. I am board certified by the American Board of Internal Medicine and American Board of Allergy and Immunology. I interned at the San Francisco General Hospital, was a resident at the University of Wisconsin Hospital, and worked as a medical doctor at the Fort Carson, Colorado, U.S. Army Hospital. In 1975, I entered private practice, and since that time have focused on the treatment of asthma and related conditions.

3. I have given over 40 professional presentations, authored or co-authored over 50 publications, and authored or co-authored over 30 abstracts concerning asthma, allergic rhinitis and drugs used to treat these and related conditions. I have also conducted numerous clinical trials to determine the safety and efficacy of drugs such as albuterol and loratadine in the treatment of asthma and allergic rhinitis. I have prescribed loratadine to hundreds of patients, and am intimately familiar with its adverse effects.

4. In sum, I am an expert in the treatment of allergies and allergic rhinitis. I have first-hand knowledge of the safety and efficacy of various drugs used to treat these conditions and the problems faced by the pharmaceutical industry in developing new drugs to treat these conditions. I am particularly familiar with loratadine and other drugs related to it, and the serious adverse effects associated with them.

5. I have read International Application No. WO96/20708, which I understand corresponds to European Patent Application No. 95943722.9 ("the Patent Application"), and what I understand to be the claims currently pending in the Patent Application. I have also read the Decision to Refuse European Patent Application No. 95943722.9, dated September

8, 2000, the art cited therein, and additional art cited in connection with the Patent Application. In particular, I have read documents D1, D2, E1-E11 and E12-E23, which are identified in Exhibit B, attached hereto.

II. HISTAMINE-INDUCED PAW EDEMA EXPERIMENTS DO NOT PROVIDE INFORMATION SUFFICIENT TO DETERMINE WHETHER A COMPOUND WOULD BE EFFECTIVE IN THE TREATMENT OF ALLERGIC RHINITIS

6. In order for a compound to be effective in treating allergic rhinitis, it must be capable of selectively preventing histamine from binding to H_1 histamine receptors. Compounds with such a capacity are referred to as antihistamines or selective H_1 antagonists.

7. At least two additional types of histamine receptor are known to exist; they are referred to as H_2 and H_3 receptors. Drugs that selectively prevent histamine binding to these receptors are known as selective H_2 and H_3 antagonists, respectively. Selective H_2 and H_3 antagonists are not capable of preventing histamine from binding to H_1 receptors, and are therefore not useful in the treatment of the allergic conditions such as allergic rhinitis.

8. By December 30, 1994, which I understand is the earliest filing date to which the Patent Application is entitled, it was well known that a variety of compounds, many of which are not selective H_1 antagonists, reduce histamine-induced paw edema in rodents. For example, it was reported in document E12 that the selective H_2 antagonists cimetidine, ranitidine and loxtidine reduce histamine-induced paw edema in rodents. Similarly, it was reported in document E13 that the selective H_2 antagonist burimamide is capable of inhibiting paw edema induced by the histamine releasing agent 48/80. Prior to December 30, 1994, it was known that these compounds are not effective antihistamines, since they are not selective H_1 antagonists. Therefore, it was known by December 30, 1994 that compounds which are not effective in the treatment of allergic conditions can inhibit histamine-induced paw edema in rodents.

9. Because of what was known about the histamine-induced paw edema test, the experiments described in document D1 would not have convinced me that the compound tested is a selective H_1 antagonist. In other words, D1 would not have convinced me that the compound tested could effectively be used to treat allergic conditions such as allergic rhinitis. Before drawing such a conclusion, I would have considered it essential to characterize the compound using one or more pharmacological models known to show anti-allergic activity. Examples of models suitable for assessing efficacy in allergic rhinitis are disclosed in documents E15, E16 and E17.

III. THE SAFETY OF A DRUG USED TO TREAT NON-LIFE-THREATENING DISEASES IS OF PARAMOUNT IMPORTANCE

10. It is imperative that drugs used to treat non-life-threatening diseases, such as allergic rhinitis, be safe. This is in contrast to drugs used to treat severe diseases, such as cancer, where the risk of adverse effects such as cardiac arrhythmia or cardiac arrest is outweighed by the severity of the disease.

11. Before December 30, 1994, I was concerned by reports that certain compounds known as "piperadine H_1 antagonists" can cause cardiovascular side effects, such as cardiac arrest, torsades de pointes, and ventricular arrhythmias. I was concerned because I did not want to expose patients who suffered from the mere discomfort of allergic rhinitis to the risk of heart arrhythmia or death.

IV. BEFORE THE EARLIEST FILING DATE OF THE PATENT APPLICATION, NO PROOF EXISTED THAT DCL WAS NOT CARDIO-TOXIC

12. Loratadine was a known H_1 antagonist, or antihistamine, before December 30, 1994. The fact that loratadine metabolizes to form the structurally similar compound descarboxyloratadine ("DCL") was also known by that time. *See, e.g.,* document D2.

13. Before the earliest filing date of the Patent Application, loratadine was considered by those skilled in the art to be a member of a class of compounds known as "piperadine H_1 antagonists," which also includes terfenadine and astemizole. The chemical and pharmacological similarities of loratadine, terfenadine and astemizole were well known by that time. This is evidenced, in part, by document E18, which is considered to be a standard work in the field of pharmacology. E18 describes loratadine in the first column on page 587 as being a member of the class piperidine H_1 antagonists. Although only one other member of class, terfenadine, is mentioned in this passage, astemizole and terfenadine are identified as members of the class in Table 23-3 on page 585. Further confirmation that loratadine, terfenadine and astemizole were considered to belong to the same class of drugs can be found on pages 583, 584 and 586 of E18.

14. In 1994, before the earliest filing date of the Patent Application, I expected DCL to share certain fundamental properties with loratadine because of the compounds' similar chemical structures and pharmacological relationship. However, it is suggested in the Decision to Refuse European Patent Application No. 95943722.9 that the chemical differences between terfenadine and astemizole, on one hand, and loratadine and DCL, on the other, are such that those skilled in the art would have expected loratadine and DCL to behave differently from terfenadine and astemizole *in vivo*. This was simply not the case in

1994. Indeed, I considered reports concerning the adverse effects of one piperadine H_1 antagonist to be relevant to the safety of other members of that class.

15. In this regard, it was well known by December 30, 1994 that very serious cardio-toxic side effects had been reported for two piperadine H_1 antagonists, terfenadine and astemizole. *See, e.g.*, documents E2 and E3. I considered it possible that these side effects, which included ventricular arrhythmia, particularly torsades de pointes, cardiac arrest and even death, could be class effects, common to all piperadine H_1 antagonists. Indeed, similar cardio-toxic side effects were reported for loratadine in document E5. Moreover, document E8 reported that loratadine and DCL interact with ketoconazole to give raised serum levels, which is precisely the effect that precipitates the cardio-toxicity of fellow class member terfenadine. *See* document E3.

16. Before the earliest filing date of the Patent Application, those skilled in the art were aware of other adverse effects associated with loratadine. For example, document E7 reported the occurrence of personality changes. More seriously, document E1 reported that both loratadine and fellow class member astemizole can promote tumor growth in animals.

17. By late 1994, I had formed the view, which I believe was commonly held by those active in the field, that cardio-toxicity is a serious side effect that is potentially associated with all piperadine H_1 antagonists. I also believed that because DCL is an active metabolite of loratadine, it might cause personality changes and promote tumour growth.

18. It is suggested in the Decision to Refuse European Patent Application No. 95943722.9 that drug interactions would not be considered a serious side effect. This is incorrect. The capacity of a drug to cause serious and sometimes fatal side effects through interactions with other drugs is, and always has been, a matter of great concern to those in the pharmaceutical industry and medical community. For example, the interaction between terfenadine and ketoconazole, reported in E3, was considered so serious by the United States Food and Drug Administration that it required the placement of a warning on terfenadine labels. *See* E3. The drug interaction was also one of the factors which led to the eventual withdrawal of terfenadine from U.S. and other markets.

19. In the Decision to Refuse European Patent Application No. 95943722.9, it is suggested that metabolites are often "just as effective as original compounds, but without some or all side effects" associated with their parent compounds. This, too, is incorrect. In fact, scientific literature suggests just the opposite.

20. For example, document E20, which is a standard text book, states on page 149 that "one of the major natural functions of drug metabolism, i.e., the formation of more polar

and water-soluble derivatives ... results in reduction of the pharmacological activity of a drug and its rapid excretion." On page 150, it is stated that "for these reasons, drug metabolism usually leads to an accelerated termination of pharmacological activity," and that "[a]lthough most drug metabolites are less biologically active than their parent compounds, in quite a few instances a more toxic metabolite is actually produced." Likewise, page 33 of document E21, which is another standard text, states that "[d]rug metabolism generally changes a drug to more water-soluble metabolites," and goes on to state that "the body can form a toxic metabolite from a less toxic drug." Moreover, "[d]rug metabolism generally produces inactive metabolites from active drugs. ... The toxicity of some compounds may be caused by a metabolite. The insecticide parathion is changed in the body to the more toxic paraoxon." Specific examples of drugs that are metabolised to inactive metabolites include epinephrine (*see* document E18, page 197), norepinephrine (*see* document E18, page 199) estrogens (*see* document E22, page 812), methylphenidate (*see* document E22, page 459), and corticosteroids (*see* document E22, page 770).

21. Particularly relevant to what was known about the toxicity of histamine metabolites is the black-box warning that the U.S. Food and Drug Administration (FDA) required be added to the label of astemizole. *See Physicians Desk Reference*, 1088-1090 (48th ed., 1994) (attached hereto as Exhibit C). The warning stated that "rare cases of serious cardiovascular adverse effects including death, cardiac arrest, QT prolongation, torsades de pointes, and other ventricular arrhythmias have been observed in patients" and that "data suggest that these events are associated with astemizole and/or astemizole metabolite levels." *Id.* (emphasis added). The warning was announced by the FDA in "Warnings Issued on Nonsedating Antihistamines and Terfenadine and Astemizole," *JAMA* 268(6):705 (1992) (attached hereto as Exhibit D), which simultaneously announced a warning for terfenadine. Consequently, in 1994, those skilled in the art understood that metabolites of piperadine H_1 antagonists could exhibit the same—or be responsible for—the serious adverse effects associated with their parent compounds.

22. In sum, safety is of paramount concern to those developing new drugs for the treatment of allergic disorders such as allergic rhinitis. Before December 30, 1994, those skilled in the art considered loratadine to be a member of a class of compounds that were known to exhibit severe adverse effects, such as ventricular arrhythmia, cardiac arrest, and death. At that time, I had no reason to expect that loratadine and DCL did not also share those same adverse effects. Consequently, I would not have considered DCL to be a safe and effective alternative to loratadine or other piperadine H_1 antagonists.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and any patent issuing thereon.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal the day and year set opposite my signature.

Dated: 10/21/03 W Storms MD L.S.

State of Colorado)
) SS.:
County of El Paso)

On 10/21/03, before me, Beth Carlisle, Notary Public, personally appeared William W. Storms, M.D., personally known to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument and acknowledged to me that, by his signature on the instrument, she executed the instrument.

WITNESS my hand and official seal

Beth A Carlisle

Exp: 8/27/07

EXHIBIT A

CURRICULUM VITAE

WILLIAM W. STORMS, M.D.

9/13/00

PERSONAL INFORMATION

Date of Birth:	May 18, 1942
Place of Birth:	Racine, Wisconsin
Spouse:	Bette
Children:	Trisha, Cathy, Jenny
Home:	3855 Hermitage Drive, Colorado Springs, CO 80906 (719) 632-2702
Offices:	Asthma & Allergy Associates 2709 N. Tejon St., Colorado Springs, CO 80907 (719) 473-0872 Fax: (719) 630-3658
	41 Montebello Rd. #202 Pueblo, CO 81001 (719) 564-2503 Fax: (719) 545-7675
E-Mail Address:	SneezeDoc@aol.com
SSN:	390-40-9558

PRESENT ACADEMIC RANK & OTHER POSITIONS

Clinical Professor of Medicine, University of Colorado Health Sciences Center, Denver, Colorado
Practicing Allergist, Asthma & Allergy Associates, P.C., Colorado Springs, CO
Co-Director, The Research Center, Asthma and Allergy Associates, Colorado Springs,CO
Member of Sports Medicine Committee of the U.S. Olympic Committee 1997 to present
IRB member, United States Olympic Committee, 1997 to present
National Asthma Education and Prevention Program Coordinating Committee, (NHLBI Asthma Guidelines) 1998 to present
Co-Chair, Professional and Patient/Public Education Subcommittee of the NAEPP 1998 to present
Representative to Task Force On Allergic Disorders: Promoting Best Practice

EDUCATION

University:	Northwestern University, Evanston, Illinois, B.A. Degree, 1964
Medical School:	University of Wisconsin Medical School, Madison, Wisconsin, M.D. Degree, 1968
Internship:	San Francisco General Hospital, San Francisco, California, 1968-69
Residency:	Internal Medicine Residency; University of Wisconsin Hospital, Madison, Wisconsin, 1969-70, 1972-73
Military Service:	U.S. Army Hospital, Fort Carson, Colorado, Allergy Service,1970-72

EDUCATION (cont.)

Fellowship:	Allergy and Immunology; University of Wisconsin Hospital, Madison, Wisconsin, 1973-75
Private Practice:	Asthma & Allergy Associates, P.C., Colorado Springs, CO, 1975 to present

BOARD CERTIFICATION

American Board of Internal Medicine, 1974
American Board of Allergy and Immunology, 1975
Recertification: American Board of Allergy and Immunology, 1987

MEDICAL LICENSURE Colorado #16815

SOCIETY MEMBERSHIPS

Fellow, American College of Physicians
Fellow, American Academy of Allergy, Asthma and Immunology
Fellow, American College of Allergy, Asthma and Immunology
Fellow, American College of Chest Physicians
Western Society of Allergy and Immunology
American Thoracic Society
Trudeau Society
Colorado Allergy Society
American Association for the Advancement of Science
European Respiratory Society
Colorado Medical Society
European Academy of Allergology and Clinical Immunology

MEMBERSHIP ON COMMITTEES; OFFICES HELD

Board of Regents Member, American College of Allergy and Immunology, 1990 to 1993

President, Colorado Allergy Society, 1990-92

President, Western Society of Allergy and Immunology, 1987-88

Chairman, Public Relations Committee, American College of Allergy and Immunology, 1988

Chairman, Bylaws Committee, Penrose Hospital, Colorado Springs, 1985 to 1988

Chairman, American Academy of Allergy and Immunology Sports Medicine Committee,1994-97

Steering Committee, American College of Chest Physicians Section on Allergy and Clinical Immunology, 1986-91

El Paso County Medical Society Delegate to the Colorado Medical Society, 1989 to 1996

Advisory Board Member of Strategic Institute, a CME provider, Vienna, Virginia, 1996 to present

Member of The Steering Committee of the Aspen Allergy Conference 1997 to present

MEDICAL JOURNAL EDITORIAL BOARD MEMBERSHIP

Annals of Allergy, Asthma and Immunology, 1993 to 1998
Journal of Asthma, 1992 to present
Pediatric Rounds Newsletter, 1996 to present

OTHER ACTIVITIES, ORGANIZATIONS, & AWARDS

Distinguished Fellow of the American College of Allergy, Asthma & Immunology. Presented at the awards convocation November 6, 1998 in Philadelphia, PA.

Bela Schick invited Lectureship, American College of Allergy, Asthma, & Immunology, Annual Meeting, San Francisco, November 1994

President, Cheyenne Mountain Zoological Park, 1991-92
Board of Trustees Member, 1987 to 1995

Vestry member, Chapel of Our Saviour Episcopal Church, Colorado Springs, 1978-81

Listed in "The Best Doctors in America: Central Region." 1996-1997.

Who's Who in Health and Medicine, 1989 to present

Student Volunteer, Project Hope, Colombia, South America, Summer 1967

Vice President, Broadmoor Ski Racing Academy, Inc., 1979-82

Volunteer Physician, Colorado Champ Camp (for children with asthma), 1985-95

PRESENTATIONS AT NATIONAL & INTERNATIONAL MEETINGS (cont.)

15. "Allergic Rhinitis" Washington University Symposium on Allergic Disease, St. Louis, November, 1990

16. "A Once-A-Day Nasal Steroid (Nasacort - triamcinolone acetonide) is Effective Therapy for Perennial Allergic Rhinitis." Presented at the Ninth Annual Aspen Allergy Conference, July 23-27, 1991, Aspen, Colorado

17. "New Therapeutic Approaches to Allergic Rhinitis," American Academy of Allergy and Immunology, March 1992; Orlando, Florida

18. "Lipoxygenase and Leukotriene Inhibitors." Presented at the 1992 American College of Allergy and Immunology Symposium entitled "A New Age In the Therapy of Allergic Diseases," November 18, 1992.

19. "Sch 1000 - An Anticholinergic Bronchodilator." Presented at the Symposium on the Parasympathetic Pathway in Obstructive Lung Disease, Killarney, Ireland, 1974

20. "Azelastine in Bronchial Asthma." Presented at the Azelastine Symposium at the International College of Allergy and Clinical Immunology, Washington, D.C., October, 1985

21. "Ipratropium in the Treatment of Asthma." Presented at the Symposium on Cholinergic Pathways in Lung Disease, Toronto, July, 1986

22. "Bronchodilator Properties of Azelastine." Azelastine Workshop - American Lung Association Meeting, New Orleans, May, 1987

23. "Azelastine: U.S. Experience in Seasonal and Perennial Rhinitis." Presented at the XIVth Congress of the European Academy of Allergology and Clinical Immunology, Berlin (West), September, 1989

24. "Effect of Repeat Action Albuterol Sulfate (Proventil® Repetabs®) in Nocturnal Asthma," presented at the XIV International Congress of Allergology and Clinical Immunology, Kyoto, Japan, October, 1991

25. "The Effect of Repeat Action Albuterol Sulfate Tablets (Proventil® Repetabs®) in the Treatment of Nocturnal Asthma," presented at the Fifth International Conference on Chronobiology, Amelia Island, Florida, July 16, 1992

26. "Rationale for the Use of Antihistamines in Allergic Rhinitis, " International Symposium of Infection and Allergy of the Nose, Seoul, Korea, October 8-11, 1993

27. "Fluticasone Nasal Spray: Comparator Studies in Allergic Rhinitis," European Academy of Allergy and Immunology, Stockholm, Sweden, June 1994

PRESENTATIONS AT NATIONAL & INTERNATIONAL MEETINGS (cont.)

28. Moderator and Discussant, Interesting Case Symposium, American College of Allergy, Asthma & Immunology, Annual Meeting, San Francisco, CA, November 1994

29. Co-Chairman of the Olympic Exercise Asthma Symposium, Colorado Springs, CO, December 2-4, 1994.

30. Diagnosis and Treatment of Asthma." Lecture at the American Academy of Family Physicians. Annual Meeting, Orlando, FL, September 1995.

31. "Exercise Asthma in Athletes." Presented at the Eastern Allergy Conference, April 18, 1995.

32. "Asthma Quality of Life Surveys in an Office Setting," ACAAI Managed Care Conference, Washington DC, April 12, 1996.

33. Chairman, United States Olympic Committee Conference on Asthma for Physicians, Coaches and Athletic Trainers, November 1996, U.S. Olympic Training Center, Colorado Springs, CO.

34. Moderator and speaker, ACAAI Annual Meeting Saturday Morning Conference, San Diego, CA.

35. Speaker, AAAAI Sunday Evening Symposium on the Treatment of Asthma, March 1998, Washington DC.

36. Luncheon moderator "Treatment of Rhinitis and Its Effects on the Lower Airway", Sunday symposium at the AAAAI meeting, Washington DC, March 1998.

37. Speaker on Exercise-Induced Asthma at the 1st Sports Medicine Conference of the Arab World, Kuwait University, Kuwait City, Kuwait, March 1998.

38. Speaker at the International Congress of Pediatric Allergy & Immunology, Cordoba, Argentina, May 24-27, 1998 ("Safety and efficacy of montelukast in children: a review of clinical data"; "Improving control of asthma in the moderately severe asthmatic".

39. "The Profile of the Ideal Nasal Steroid" at the European Academy of Allergy and Clinical Immunology Meeting, Brussels, Belgium, July, 1999

40. "Exercise Induced Asthma", presented at Cornell Medical College Allergy Teaching Day, New York, NY, October, 1999.

41. "Asthma and Rhinitis", presented at the American College of Allergy, Asthma and Immunology Annual Meeting, Chicago, IL, November, 1999.

CLINICAL TRIALS PERFORMED AT THE RESEARCH CENTER

Ipratropium bromide inhaler for the treatment of asthma - various studies, 1975-1990
Flunisolide inhaler for the treatment of asthma - 1977
Tazifyline tablets in rhinitis - 1987
Albuterol inhalant solution for asthma - 1984
Ketotifen syrup for children in asthma - 1984-1987
Procaterol inhaler for asthma - various studies - 1984-1990

CLINICAL TRIALS PERFORMED AT THE RESEARCH CENTER (cont.)

Alupent inhaler for children with asthma - 1985-1989
Triamcinolone nasal spray for the treatment of rhinitis - various studies, 1986-1991
Loratadine and loratadine decongestant tablet studies for the treatment of rhinitis – 1986 to 1995
Tazifyline tablets in rhinitis - 1987
Enprofylline tablets for asthma - 1987
Proventil Repetabs for asthma - 1987-1989, 1992
Budesonide inhaler for asthma and rhinitis - 1987, 1991-1995
Efficacy of azelastine in perennial allergic rhinitis - 1988
Intal MDI for asthma - 1988
MK 571 capsules for asthma - 1989
Accolate inhaler and tablet for asthma - 1989-1995
Auranofin capsules for steroid dependent asthmatics - 1989-1990
Nedocromil inhalant solution for children with asthma - 1990
Salmeterol inhaler for asthma - 1990-1995, 1997
SCH 37370 tablet for rhinitis - 1990-91
Azelastine nasal spray for rhinitis - 1990
Vancenase-AQ vs. Nasalcrom in allergic rhinitis (pediatric) - 1990
Triamcinolone nasal spray (Nasacort) in allergic rhinitis (pediatric) - 1990
Pemirolast - 1991
Oral ebastine for allergic rhinitis – 1991-1998
Formeterol in Asthma - 1992
MK-0591 for asthma - 1992-1993
Vanceril DS - 1992-1993
Zileuton in Asthma - 1992, 1994, 1997
Fluticasone in Asthma and Rhinitis Adult and Pediatric - 1992-1995, 1997, 1998
Albuterol Turbuhaler - 1993
CP-80633 Tablet for Asthma - 1993
RP-73401 in Asthma - 1993
Uniphyl vs Beclovent - 1993
Non-CFC Salbutamol - 1993
MK-0476 in adults & pediatrics for asthma – 1993-1999
Mometasone in Asthma and Rhinitis - 1993-1994, 1997-1998, 1999
rhu-IL-IR and rhu-IL-4R in Asthma - 1993-1994, 1999
Ceftibuten in Sinusitis - 1993-1994
Azelastine in Asthma - 1993-1995
Cetirizine in Allergic Rhinitis – 1994, 1997-1998
HOE 140 in Asthma – 1994
Nasacort Prophylaxis in Allergic Rhinitis - 1994
PDA-641 Capsules in Asthma – 1994-1996
Terfenadine and Metabolite in Rhinitis - 1994
Non-CFC Beclomethasone - 1994-1995, 1997-1998
Patient Compliance with Bronchodilator Therapy in Asthma – 1994
Atrovent in Allergic Rhinitis - 1994-1995
Effects of Vancenase on Growth - 1994
M94-216 in adult asthma - 1995
Non-CFC Azmacort in adults with asthma - 1995
Accolate in pediatric patients with asthma – 1995-1998

CLINICAL TRIALS PERFORMED AT THE RESEARCH CENTER (cont.)

Accolate in adults with asthma – 1995-1998
SB205312 in adults with allergic rhinitis - 1995
SB205312 in adults with asthma – 1995
SR 27417A in adults with asthma – 1995-1996
AA 2414 in adults with asthma – 1995
Budesonide nebulizing solution – 1995-1996
Atrovent nasal spray in adults with rhinitis – 1995
Fluticasone in sinusitis – 1996-present
BAYx7195 in adults with asthma – 1996
Double-strength beclomethasone nasal spray in adults with asthma and rhinitis – 1996
RPR 106541T in adults with asthma – 1996
D7193 in adults with asthma – 1996
RG50294 in adults with rhinitis – 1996
Non-CFC Intal in exercise-induced asthma – 1997
Fexofenadine in adults and pediatrics in rhinitis – 1994-1995, 1997
Fexofenadine in adult urticaria – 1996-1997
SB 207499 in adult COPD – 1997
Serevent in adult COPD – 1997-1998
Raxar in adult sinusitis – 1997-1998
Tiotropium in adult asthma – 1997
Norestemizole in allergic rhinitis – 1997
Zanamavir in influenza – 1998, 1999
Seratrodast in adult COPD – 1997
Seratrodast in adult asthma – 1996
MK-0966 in adults with osteoarthritis – 1997-1999
MK-0663 in adults with osteoarthritis – 1998 to present
Salmeterol/fluticasone in COPD – 1998-1999
Azelastine in vasomotor rhinitis – 1999
HMR 3647A in adult sinusitis – 1998-1999
Astra AR-C68397AA in COPD – 1998-1999
Fluticasone versus zafirlukast in asthma – 1998-1999
Salmeterol/fluticasone in adult asthma – 1998-1999
Merck L-808,065 in adult asthma – 1998-1999
Deslorafadine in adult rhinitis and asthma – 1999
Montelukast in adults with rhinitis and asthma – 1999
Effects of nasal fluticasone on growth – 1999
Effects of Accolate on growth – 1999
Effects of Azmacort on growth – 1999
Lansoprazole in adults with asthma and GERD – 1999
Montelukast in exercise-induced asthma in adults and pediatrics – 1999
Accolate in pediatric exercise-induced asthma – 1999
Effect of Rhinocort on growth – 1999

PUBLICATIONS

1. Chloroform parties, Storms WW, JAMA 225:160-165, July 9, 1973.

2. Aerosol Sch 1000: an anticholinergic bronchodilator, Storms W, DoPico G, and Reed CE, Amer Review of Resp Dis, 111:149, April 1975.

3. Alternaria IgG precipitins and adverse reactions, Busse WW, Storms WW, Crandal M, and Reed CE, J Allergy Clin Immunol, 57:367, April 1976.

4. Antibody-dependent cellular cytotoxicity in asthmatics, Flaherty DK, Martin JM, Storms WW, Kriz RJ, Surfus JE and Reed CE, J Allergy Clin Immunol, 59:48-53, 1977.

5. Occupational hypersensitivity lung disease, Storms WW, J of Occupational Med, 20:823-824, 1978.

6. Allergic reactivity of the Pikes Peak region, Storms WW, Southern Med Journal, 72:673-675, June 1979.

7. Miller moth asthma, Storms WW, Berry C, and Withee W, Clin Allergy, 11:55-59, January 1981.

8. Hay fever symptoms from the cotton of the cottonwood tree, Storms WW, Ann Allergy, 53:223-225, September 1984.

9. Albuterol nebulizer solution for the treatment of asthma, Storms WW, Hudson LD, DeGraff AC, Mendelson LM, Greenstein S, Ann Allergy, 55:779-782, December 1985.

10. Ipratropium bromide (Atrovent ^{R}): A new anticholinergic bronchodilator for the treatment of asthma, Storms WW, Immunol Allergy Practice, Vol III, P 53-59, February 1986.

11. Bitolterol mesylate aerosol in adults with steroid-dependent asthma: A comparison with isoproterenol hydrochloride aerosol, Nathan RA, Bodman SF, Storms WW, Mingo TS, Ann Allergy, 56:494-499, June 1986.

12. Use of ipratropium bromide in asthma: Results of a multi-clinic study, Storms WW, Bodman SF, Nathan RA, Busse WW, Bush RK, Falliers CJ, O'Hollaren JD, and Weg JG, Amer J Med, 81:61-66 (suppl 5A), November 1986.

13. SCH: 434; A new antihistamine/decongestant for seasonal allergic rhinitis, Storms WW, Bodman SF, Nathan RA, Chervinsky P, Banov CH, Dockhorn RJ, Jarnoszuk I, Zeitz HJ, McGeady SJ, Pinnas JL, Greenstein S, J Allergy Clin Immunol, June 1989, Vol 83, No.6:1083-1090.

14. Procaterol metered-dose inhaler: A multiclinic study evaluating the efficacy and safety in patients with asthma, Storms WW, Chervinsky P, Bell T, Kemp JP, Brandon ML, Reed CE, Siegel SC, Repsher L, Ann Allergy, 63:444-448, November 1989.

PUBLICATIONS (cont.)

15. Evaluation of the safety and efficacy of multiple doses of Azelastine to adult patients with bronchial asthma over time, Tinkelman EG, Bucholtz GA, Kemp JP, Koepke JW, Repsher LH, Spector SL, Storms WW, vanAs A, Am Rev Resp Dis, 141:569-574, 1990.

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EXHIBIT C

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Treatment: ERGAMISOL, administered orally, should be initiated no earlier than 7 and no later than 30 days post surgery at a dose of 50 mg q8h × 3 days repeated every 14 days for 1 year. Fluorouracil therapy should be initiated no earlier than 21 days and no later than 35 days after surgery providing the patient is out of the hospital, ambulatory, maintaining normal oral nutrition, has well-healed wounds, and is fully recovered from any postoperative complications. If ERGAMISOL has been initiated from 7 to 20 days after surgery, initiation of fluorouracil therapy should be coincident with the second course of ERGAMISOL, i.e., at 21 to 34 days. If ERGAMISOL is initiated from 21 to 30 days after surgery, fluorouracil should be initiated simultaneously with the first course of ERGAMISOL.

Fluorouracil should be administered by rapid IV push at a dosage of 450 mg/m²/day for 5 consecutive days. Dosage calculation is based on actual weight (estimated dry weight if there is evidence of fluid retention). *This course should be discontinued before the full 5 doses are administered if the patient develops any stomatitis or diarrhea* (5 or more loose stools). Twenty-eight days after initiation of this course, weekly fluorouracil should be instituted at a dosage of 450 mg/m²/week and continued for a total treatment time of 1 year. If stomatitis or diarrhea develop during weekly therapy, the next dose of fluorouracil should be deferred until these side effects have subsided. If these side effects are moderate to severe, the fluorouracil dose should be reduced 20% when it is resumed.

Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm³ defer the fluorouracil dose until WBC is > 3500/mm³. If WBC is < 2500/mm³, defer the fluorouracil dose until WBC is > 3500/mm³; then resume the fluorouracil dose reduced by 20%. If WBC remains < 2500/mm³ for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless platelets are adequate (≥ 100,000/mm³).

ERGAMISOL should not be used at doses exceeding the recommended dose or frequency. Clinical studies suggest a relationship between ERGAMISOL adverse experiences and increasing dose, and since some of these, e.g. agranulocytosis, may be life-threatening, the recommended dosage regimen should not be exceeded (see "WARNINGS").

Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.

HOW SUPPLIED

ERGAMISOL (levamisole hydrochloride) is available in white, coated tablets containing the equivalent of 50 mg of levamisole base, debossed "JANSSEN" and "L"/"50". They are supplied in blister packages of 36 tablets (NDC 50458-270-36).

Store at room temperature, 15°–30°C (59°–86°F).
Protect from moisture.

Adverse experience	ERGAMISOL N = 440 %	ERGAMISOL plus fluorouracil N = 599 %
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
< 2000/mm³	<1	1
≥ 2000 to < 4000/mm³	4	19
≥ 4000/mm³	2	33
unscored category	0	<1
Thrombocytopenia		
< 50,000/mm³	0	0
≥ 50,000 to < 130,000/mm³	1	8
≥ 130,000/mm³	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5
Rigors	3	5
Chest pain	<1	1
Edema	1	1
Resistance Mechanisms		
Infection	5	12
Special Senses		
Taste Perversion	8	8
Altered sense of smell	1	1
Musculoskeletal System		
Arthralgia	5	4
Myalgia	3	2
Central and peripheral nervous system		
Dizziness	3	4
Headache	3	4
Paresthesia	2	3
Ataxia	0	2
Psychiatric		
Somnolence	3	2
Depression	1	2
Nervousness	1	2
Insomnia	1	1
Anxiety	1	1
Forgetfulness	0	1
Vision		
Abnormal tearing	0	4
Blurred vision	1	2
Conjunctivitis	<1	2
Liver and biliary system		
Hyperbilirubinemia	<1	1

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Edition January 1993, February 1993
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HISMANAL®

[*his'ma-nal*]
(astemizole) Tablets

DESCRIPTION

HISMANAL® (astemizole) is a histamine H_1-receptor antagonist available in scored white tablets for oral use. Each tablet contains 10 mg of astemizole, and, as inactive ingredients: lactose, cornstarch, microcrystalline cellulose, pregelatinized starch, povidone K90, magnesium stearate, colloidal silicon dioxide, and sodium lauryl sulfate. Astemizole is chemically designated as 1-[(4-fluorophenyl)-methyl]-*N*-[1-[2-(4-methoxyphenyl)ethyl] -4- piperidinyl]-1*H*-benzimidazol-2-amine, with a molecular weight of 458.58. The empirical formula is $C_{28}H_{31}FN_4O$.

Astemizole is a white to slightly off-white powder; it is insoluble in water, slightly soluble in ethanol and soluble in chloroform and methanol.

CLINICAL PHARMACOLOGY

HISMANAL is a long-acting, selective histamine H_1-receptor antagonist. Receptor binding studies in animals demonstrated that at pharmacological doses, HISMANAL occupies peripheral H_1-receptors but does not reach H_1-receptors in the brain. Whole body autoradiographic studies in rats, radiolabel tissue distribution studies in dogs and radioligand binding studies of guinea pig brain H_1-receptors have shown that HISMANAL does not readily cross the blood-brain barrier. Screening studies in rats at effective antihistaminic doses showed no anticholinergic effects. Studies in humans using the recommended dosage regimens have not been performed to determine whether HISMANAL is associated with a different frequency of anticholinergic effects than therapeutic doses of other antihistamines.

The absorption of HISMANAL is reduced by 60% when taken with meals. In single oral dose studies, HISMANAL was rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of unchanged HISMANAL were reached within one hour. Due to extensive first pass metabolism and significant tissue distribution, plasma concentrations of unchanged drug were low. Elimination of unchanged HISMANAL occurred with a half-life of approximately one day. Elimination of HISMANAL plus hydroxylated metabolites, considered together to represent the pharmacologically active fraction in plasma, was biphasic with half-lives of 20 hours for the distribution phase and 7–11 days for the elimination phase. The pharmacokinetics of HISMANAL plus hydroxylated metabolites are dose proportional following single doses of 10 to 30 mg.

Following chronic administration, steady state plasma concentrations of HISMANAL plus hydroxylated metabolites (mainly desmethylastemizole) were reached within four to eight weeks; concentrations of the metabolites are substantially higher than those of unchanged HISMANAL. HISMANAL plus hydroxylated metabolites decayed biphasically with an initial half-life of 7–9 days, with plasma concentrations being reduced by 75% within this phase, and with a terminal half-life of about 19 days. The initial phase ($t_{1/2}$ = 7–9 days) appears to determine the time to reach steady state plasma concentrations of HISMANAL plus hydroxylated metabolites. Steady state plasma concentrations of unchanged HISMANAL were reached by 6 days (with a range of 6–8 days); unchanged HISMANAL was eliminated from plasma with a half-life of approximately 2 days (with a range of 1–2.5 days).

Excretion and metabolism studies with ^{14}C-labeled HISMANAL in volunteers demonstrated that the drug is

almost completely metabolized in the liver and pr... excreted in the feces.

Interpatient variability in pharmacokinetic parameters may be greater in patients with liver disease as compared to normal subjects. Systematic evaluation of the pharmacokinetics in patients with hepatic or renal dysfunction has not been performed.

The in-vitro plasma protein binding of unchanged HISMANAL (100 ng/mL) was 96.7% with 2.3% being found as free drug in the plasma water. In human blood with an astemizole concentration of 100 ng/mL, 81.5% of astemizole was bound to the plasma proteins, with 36.2% being distributed to the blood cell fraction. The concentration of astemizole found in the blood was the same as that found in the plasma fraction of the blood. Binding studies for the astemizole metabolite(s) which achieve much higher concentrations than astemizole under chronic dosing conditions have not been conducted.

INDICATIONS AND USAGE

HISMANAL tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. HISMANAL should not be used as a p r n product for immediate relief of symptoms. Patients should be advised not to increase the dose in an attempt to accelerate the onset of action.

Clinical studies have not been conducted to evaluate the effectiveness of HISMANAL in the common cold.

CONTRAINDICATIONS

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH ERYTHROMYCIN IS CONTRAINDICATED BECAUSE ERYTHROMYCIN IS KNOWN TO IMPAIR THE CYTOCHROME P450 ENZYME SYSTEM WHICH ALSO INFLUENCES ASTEMIZOLE METABOLISM. THERE HAVE BEEN TWO REPORTS TO DATE OF SYNCOPE WITH TORSADES DE POINTES, REQUIRING HOSPITALIZATION, IN PATIENTS TAKING COMBINATIONS OF HISMANAL 10 MG DAILY WITH ERYTHROMYCIN. IN EACH CASE THE QT INTERVALS WERE PROLONGED BEYOND 650 MILLISECONDS AT THE TIME OF THE EVENT; ONE PATIENT ALSO RECEIVED KETOCONAZOLE AND THE OTHER PATIENT ALSO HAD HYPOKALEMIA.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH KETOCONAZOLE TABLETS IS CONTRAINDICATED BECAUSE AVAILABLE HUMAN PHARMACOKINETIC DATA INDICATE THAT ORAL KETOCONAZOLE SIGNIFICANTLY INHIBITS THE METABOLISM OF ASTEMIZOLE, RESULTING IN ELEVATED PLASMA LEVELS OF ASTEMIZOLE AND DESMETHYLASTEMIZOLE. DATA SUGGEST THAT CARDIOVASCULAR EVENTS ARE ASSOCIATED WITH ELEVATION OF ASTEMIZOLE AND/OR ASTEMIZOLE METABOLITE LEVELS, RESULTING IN ELECTROCARDIOGRAPHIC QT PROLONGATION.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH ITRACONAZOLE IS ALSO CONTRAINDICATED BASED ON THE CHEMICAL RESEMBLANCE OF ITRACONAZOLE AND KETOCONAZOLE. IN-VITRO DATA SUGGEST THAT ITRACONAZOLE HAS A LESS PRONOUNCED EFFECT ON THE BIOTRANSFORMATION SYSTEM RESPONSIBLE FOR THE METABOLISM OF ASTEMIZOLE COMPARED TO KETOCONAZOLE. (See WARNINGS and PRECAUTIONS: Drug Interactions.)

HISMANAL is contraindicated in patients with known hypersensitivity to astemizole or any of the inactive ingredients.

WARNINGS

QT PROLONGATION/VENTRICULAR ARRHYTHMIAS

RARE CASES OF SERIOUS CARDIOVASCULAR ADVERSE EVENTS INCLUDING DEATH, CARDIAC ARREST, QT PROLONGATION, TORSADES DE POINTES, AND OTHER VENTRICULAR ARRHYTHMIAS HAVE BEEN OBSERVED IN PATIENTS EXCEEDING RECOMMENDED DOSES OF ASTEMIZOLE. WHILE THE MAJORITY OF SUCH EVENTS HAVE OCCURRED FOLLOWING SUBSTANTIAL OVERDOSES OF ASTEMIZOLE, TORSADES DE POINTES (ARRHYTHMIAS) HAVE VERY RARELY OCCURRED AT REPORTED DOSES AS LOW AS 20-30 MG DAILY (2-3 TIMES THE RECOMMENDED DAILY DOSE). DATA SUGGEST THAT THESE EVENTS ARE ASSOCIATED WITH ELEVATION OF ASTEMIZOLE AND/OR ASTEMIZOLE METABOLITE LEVELS, RESULTING IN ELECTROCARDIOGRAPHIC QT PROLONGATION. THESE EVENTS HAVE ALSO OCCURRED AT 10 MG DAILY IN A FEW PATIENTS WITH POSSIBLE AUGMENTING CIRCUMSTANCES (SEE CONTRAINDICATIONS, AND WARNING PARAGRAPHS BELOW WARNINGS BOX). IN VIEW OF THE POTENTIAL FOR CARDIAC ARRHYTHMIAS, ADHERENCE TO THE RECOMMENDED DOSE SHOULD BE EMPHASIZED. DO NOT EXCEED THE RECOMMENDED DOSE OF 10 MG (ONE TABLET) DAILY.

SOME PATIENTS APPEAR TO INCREASE THE DOSE OF HISMANAL IN AN ATTEMPT TO ACCELERATE THE ONSET OF ACTION. PATIENTS SHOULD BE ADVISED NOT TO DO THIS AND NOT TO USE HISMANAL AS A P R N PRODUCT FOR IMMEDIATE RELIEF OF SYMPTOMS.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH KETOCONAZOLE TABLETS, ITRACONAZOLE, OR ERYTHROMYCIN IS CONTRAINDICATED. (SEE CONTRAINDICATIONS AND PRECAUTIONS: DRUG INTERACTIONS.)

SINCE ASTEMIZOLE IS EXTENSIVELY METABOLIZED BY THE LIVER, THE USE OF ASTEMIZOLE IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION SHOULD GENERALLY BE AVOIDED.

IN SOME CASES, SEVERE ARRHYTHMIAS HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. SYNCOPE IN PATIENTS RECEIVING ASTEMIZOLE SHOULD LEAD TO IMMEDIATE DISCONTINUATION OF TREATMENT AND APPROPRIATE CLINICAL EVALUATION, INCLUDING ELECTROCARDIOGRAPHIC TESTING (LOOKING FOR QT PROLONGATION AND VENTRICULAR ARRHYTHMIA). (SEE CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, AND DOSAGE AND ADMINISTRATION.)

Patients known to have conditions leading to QT prolongation may experience QT prolongation and/or ventricular arrhythmia with astemizole at recommended doses. The effect of astemizole in patients who are receiving agents which alter the QT interval is unknown. However, in view of astemizole's known potential for QT prolongation, it is advisable to avoid its use in patients with QT prolongation syndrome or who are taking medications which are reported to prolong QT intervals (including probucol, certain antiarrhythmics, certain tricyclic antidepressants, certain phenothiazines, certain calcium channel blockers such as bepridil, and terfenadine), patients with electrolyte abnormalities such as hypokalemia or hypomagnesemia, or those taking diuretics with potential for inducing electrolyte abnormalities.

Rare cases of cardiovascular events have been observed in patients with hepatic dysfunction. Systematic evaluation of the pharmacokinetics of astemizole in patients with hepatic dysfunction has not been performed. Since astemizole is extensively metabolized by the liver, the use of HISMANAL in patients with significant hepatic dysfunction should generally be avoided.

PRECAUTIONS

General:

Caution should be given to potential anticholinergic (drying effects) in patients with lower airway diseases.

Caution should be used in patients with cirrhosis or other liver diseases. (See CLINICAL PHARMACOLOGY section.)

HISMANAL does not appear to be dialyzable.

Caution should also be used when treating patients with renal impairment.

Drug Interactions:

See CONTRAINDICATIONS and WARNINGS sections for discussion of information regarding potential drug interactions.

Ketoconazole/Itraconazole

Concomitant administration of ketoconazole tablets or itraconazole with astemizole is contraindicated. (See CONTRAINDICATIONS and WARNINGS BOX.)

Due to the chemical similarity of fluconazole, metronidazole, and miconazole i.v. to ketoconazole, concomitant use of these products with astemizole is not recommended.

Macrolides (including erythromycin)

Concomitant administration of erythromycin with astemizole is contraindicated. (See CONTRAINDICATIONS and WARNINGS BOX.) Concomitant administration of astemizole with other macrolide antibiotics, including troleandomycin, azithromycin, and clarithromycin, is not recommended.

Information for Patients:

Patients taking HISMANAL should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients taking HISMANAL should be advised 1) to adhere to the recommended dose, and 2) that the use of excessive doses may lead to serious cardiovascular events. Some patients appear to increase the dose of HISMANAL in an attempt to accelerate the onset of action. PATIENTS SHOULD BE ADVISED NOT TO DO THIS and not to use HISMANAL as a p r n product for immediate relief of symptoms. Patients should be questioned about use of any other prescription or over-the-counter medication, and should be cautioned regarding the potential for life-threatening arrhythmias with concurrent use of ketoconazole, itraconazole, or erythromycin. Patients should be advised to consult the physician before concurrent use of other med... tions with astemizole. Patients should be questioned ab... pregnancy or lactation before starting HISMANAL ther... since the drug should be used in pregnancy or lactation o... if the potential benefit justifies the potential risk to fetu... baby. (See Pregnancy subsection.) In addition, patie... should be instructed to take HISMANAL on an empty st... ach, e.g., at least 2 hours after a meal. No additional f... should be taken for at least 1 hour after dosing. Patie... should also be instructed to store this medication in a tigh... closed container in a cool, dry place, away from heat or dir... sunlight, and away from children.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenic potential has not been revealed in rats giv... 260× the recommended human dose of astemizole ... 24 months, or in mice given 400× the recommended hum... dose for 18 months. Micronucleus, dominant lethal, sis... chromatid exchange and Ames tests of astemizole have ... revealed mutagenic activity.

Impairment of fertility was not observed in male or fem... rats given 200× the recommended human dose.

Pregnancy: Pregnancy Category C:

Teratogenic effects were not observed in rats administe... 200× the recommended human dose or in rabbits giv... 200× the recommended human dose. Maternal toxicity w... seen in rabbits administered 200× the recommended h... man dose. Embryocidal effects accompanied by materr... toxicity were observed at 100× the recommended hum... dose in rats. Embryotoxicity or maternal toxicity was ... observed in rats or rabbits administered 50× the reco... mended human dose. There are no adequate and well co... trolled studies in pregnant women. HISMANAL should ... used during pregnancy only if the potential benefit justifi... the potential risk to the fetus. Metabolites may remain in t... body for as long as 4 months after the end of dosing, calc... lated on the basis of 6 times the terminal half-life. (S... CLINICAL PHARMACOLOGY section.)

Nursing Mothers:

It is not known whether this drug is excreted in human mil... Because certain drugs are known to be excreted in hum... milk, caution should be exercised when HISMANAL ... administered to a nursing woman. HISMANAL is excret... in the milk of dogs.

Pediatric Use:

Safety and efficacy in children under 12 years of age has n... been demonstrated.

ADVERSE REACTIONS

For information regarding cardiovascular adverse event... (e.g. cardiac arrest, ventricular arrhythmias), please se... CONTRAINDICATIONS and WARNINGS BOX. In some... cases, recognition of severe arrhythmias has been precede... by episodes of syncope. Similarly, rare cases of hypotension... palpitations, and dizziness have also been reported wit... HISMANAL use, which may reflect undetected ventricula... arrhythmia.

The reported incidences of adverse reactions listed in th... following table are derived from controlled clinical studies i... adults. In these studies the usual maintenance dose ... HISMANAL was 10 mg once daily.

[See table on next page.]

Adverse reaction information has been obtained from mor... than 7500 patients in all clinical trials. Weight gain has bee... reported in 3.6% of astemizole treated patients involved i... controlled studies, with an average treatment duration o... 53 days. In 46 of the 69 patients for whom actual weight gai... data was available, the average weight gain was 3.2 kg.

Less frequently occurring adverse experiences reported i... clinical trials or spontaneously from marketing experienc... with HISMANAL include: angioedema, asymptomatic live... enzyme elevations, bronchospasm, depression, edema, epi... staxis, hepatitis, myalgia, palpitation, paresthesia, photosen... sitivity, pruritus, and rash.

Marketing experiences include isolated cases of convulsions... A causal relationship with HISMANAL has not been... established.

OVERDOSAGE

In the event of overdosage, supportive measures including... gastric lavage and emesis should be employed. Substantial... overdoses of HISMANAL can cause death, cardiac arrest, QT... prolongation, torsades de pointes, and other ventricular ar... rhythmias. These events can also occur, although rarely, ... at doses (20–30 mg) close to the recommended dose... (10 mg/daily). (See WARNINGS BOX and DOSAGE AND... ADMINISTRATION.)

Seizures and syncope have also been reported with overdose... and may be associated with a cardiac event.

Overdose patients should be carefully monitored as long as... the QT interval is prolonged or arrhythmias are present. In... some cases, this has been up to six days. In overdose cases in... which ventricular arrhythmias are associated with signifi... cant QT prolongation, treatment with antiarrhythmics

Continued on next page

Janssen Pharmaceutica—Cont.

ADVERSE EVENT	Percent of Patients Reporting — Controlled Studies* HISMANAL (N = 1630) %	PLACEBO (N = 1109) %	CLASSICAL** (N = 304) %
Central Nervous System			
Drowsiness	7.1	6.4	22.0
Headache	6.7	9.2	3.3
Fatigue	4.2	1.6	11.8
Appetite increase	3.9	1.4	0.0
Weight increase	3.6	0.7	1.0
Nervousness	2.1	1.2	0.3
Dizzy	2.0	1.8	1.0
Gastrointestinal System			
Nausea	2.5	2.9	1.3
Diarrhea	1.8	2.0	0.7
Abdominal pain	1.4	1.2	0.7
Eye, Ear, Nose, and Throat			
Mouth dry	5.2	3.8	7.9
Pharyngitis	1.7	2.3	0.3
Conjunctivitis	1.2	1.2	0.7
Other			
Arthralgia	1.2	1.6	0.0

*Duration of treatment in Controlled Studies ranged from 7 to 182 Days
**Classical Drugs: Clemastine (N = 137); Chlorpheniramine (N = 100); Pheniramine Maleate (N = 47); d-Chlorpheniramine (N = 20)

known to prolong QT intervals is not recommended. HISMANAL does not appear to be dialyzable.
Oral LD_{50} values for HISMANAL were 2052 mg/kg in mice and 3154 mg/kg in rats. In neonatal rats, the oral LD_{50} was 905 mg/kg in males and 1235 mg/kg in females.

DOSAGE AND ADMINISTRATION

The recommended dosage for adults and children 12 years of age and older is 10 mg (1 tablet) once daily.
DO NOT EXCEED THE RECOMMENDED DOSE. Patients should be advised not to increase the dose of HISMANAL in an attempt to accelerate the onset of action. (See WARNINGS BOX.) USE OF HISMANAL IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, OR ERYTHROMYCIN IS CONTRAINDICATED. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.)
Studies evaluating the need for dosage adjustments for patients with hepatic or renal dysfunction have not been performed. Since astemizole is extensively metabolized by the liver, use of HISMANAL in patients with significant hepatic dysfunction should generally be avoided.
HISMANAL should be taken on an empty stomach, e.g., at least two hours after a meal. There should be no additional food intake for at least one hour post-dosing.

HOW SUPPLIED

HISMANAL is available as white, scored tablets containing 10 mg of astemizole debossed "JANSSEN" and on the reverse side debossed "AST/10".
NDC 50458-510-10
(100 tablets)
Store tablets at room temperature (59°–86°F) (15°–30°C).
Protect from moisture.
U.S. Patent 4,219,559
Revised February 1992, October 1992
JANSSEN PHARMACEUTICA INC.
Titusville, New Jersey 08560-0200
Shown in Product Identification Section, page 312

IMODIUM® Ⓡ
(loperamide HCl) Capsules

DESCRIPTION

IMODIUM (loperamide hydrochloride), 4-(p-chlorophenyl)-4-hydroxy-N, N-dimethyl- α,α-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.
IMODIUM is available in 2 mg capsules.
The inactive ingredients are:
Lactose, cornstarch, talc, and magnesium stearate.
IMODIUM capsules contain F D & C Yellow No. 6.

CLINICAL PHARMACOLOGY

In vitro and animal studies show that IMODIUM acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. IMODIUM inhibits peristaltic activity by a direct effect on the circular and longitudinal muscles of the intestinal wall.
In man, IMODIUM prolongs the transit time of the intestinal contents. It reduces the daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Tolerance to the antidiarrheal effect has not been observed.
Clinical studies have indicated that the apparent elimination half-life of loperamide in man is 10.8 hours with a range of 9.1–14.4 hours. Plasma levels of unchanged drug remain below 2 nanograms per ml after the intake of a 2 mg capsule of IMODIUM. Plasma levels are highest approximately five hours after administration of the capsule and 2.5 hours after the liquid. The peak plasma levels of loperamide were similar for both formulations. Of the total excreted in urine and feces, most of the administered drug was excreted in feces. In those patients in whom biochemical and hematological parameters were monitored during clinical trials, no trends toward abnormality during IMODIUM therapy were noted. Similarly, urinalyses, EKG and clinical ophthalmological examinations did not show trends toward abnormality.

INDICATIONS AND USAGE

IMODIUM is indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. IMODIUM is also indicated for reducing the volume of discharge from ileostomies.

CONTRAINDICATIONS

IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS

IMODIUM should not be used in the case of acute dysentery, which is characterized by blood in stools and high fever.
Fluid and electrolyte depletion often occur in patients who have diarrhea. In such cases, administration of appropriate fluid and electrolytes is very important. The use of IMODIUM does not preclude the need for appropriate fluid and electrolyte therapy.
In some patients with acute ulcerative colitis, and in pseudomembranous colitis associated with broad-spectrum antibiotics, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention, constipation, or ileus occurs.
IMODIUM should be used with special caution in young children because of the greater variability of response in this age group. Dehydration, particularly in younger children, may further influence the variability of response to IMODIUM.

PRECAUTIONS

General: In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.
Patients with hepatic dysfunction should be monitored closely for signs of CNS toxicity because of the apparent large first pass biotransformation.
Information for Patients: Patients should be advised to check with their physician if their diarrhea does not improve after a couple of days or if they note blood in their stools or develop a fever.
Drug Interactions: There was no evidence in clinical trials of drug interactions with concurrent medications.
Carcinogenesis, mutagenesis, impairment of fertility: In an 18-month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis), there was no evidence of carcinogenesis. Mutagenicity studies were not conducted. Reproduction studies in rats indicated that high doses (150–200 times the human dose) could cause marked female infertility and reduced male fertility.
Pregnancy
Teratogenic Effects
Pregnancy Category B: Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus at doses up to 30 times the human dose. Higher doses impaired the survival of mothers and nursing young. The studies offered no evidence of teratogenic activity. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IMODIUM is administered to a nursing woman.
Pediatric Use: See the "Warnings" Section for information on the greater variability of response in this age group.
In case of accidental overdosage of IMODIUM by children, see "Overdosage" Section for suggested treatment.

ADVERSE REACTIONS

The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.
The following patient complaints have been reported and are listed in decreasing order of frequency with the exception of hypersensitivity reactions which is listed first since it may be the most serious.

- Hypersensitivity reactions (including skin rash) have been reported with IMODIUM use.
- Abdominal pain, distention or discomfort
- Nausea and vomiting
- Constipation
- Tiredness
- Drowsiness or dizziness
- Dry mouth

In postmarketing experiences, there have been rare reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdose, and with very young children of less than two years of age.

DRUG ABUSE AND DEPENDENCE

Abuse: A specific clinical study designed to assess the abuse potential of loperamide at high doses resulted in a finding of extremely low abuse potential.
Dependence: Studies in morphine-dependent monkeys demonstrated that loperamide hydrochloride at doses above those recommended for humans prevented signs of morphine withdrawal. However, in humans, the naloxone challenge pupil test, which when positive indicates opiate-like effects, performed after a single high dose, or after more than two years of therapeutic use of IMODIUM, was negative. Orally administered IMODIUM (loperamide formulated with magnesium stearate) is both highly insoluble and penetrates the CNS poorly.

OVERDOSAGE

In case of overdosage, paralytic ileus and CNS depression may occur. Children may be more sensitive to CNS effects than adults. Clinical trials have demonstrated that a slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed into the systemic circulation by as much as ninefold. If vomiting occurs spontaneously upon ingestion, a slurry of 100 gms of activated charcoal should be administered orally as soon as fluids can be retained.
If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gms of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. Children may be more sensitive to central nervous system effects than adults. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone.
In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Since relatively little drug is excreted in the urine, forced diuresis is not expected to be effective for IMODIUM overdosage.
In clinical trials an adult who took three 20 mg doses within a 24 hour period was nauseated after the second dose and vomited after the third dose. In studies designed to examine the potential for side effects, intentional ingestion of up to 60

EXHIBIT D

Warnings Issued on Nonsedating Antihistamines Terfenadine and Astemizole:

Terfenadine: Health professionals have been notified by Mailgram that a box warning and contraindications have been added to the labeling for terfenadine antihistamine products, Seldane and Seldane-D (Marion Merrell Dow Inc, Kansas City, Mo), regarding new information on the risk of serious cardiovascular events in patients taking terfenadine.

The warning states that rare cases of serious cardiovascular adverse events, including death, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have occurred in the following clinical settings, frequently in association with increased terfenadine levels, which lead to electrocardiographic QT prolongation: (1) concomitant administration of ketoconazole (Nizoral, Janssen Pharmaceutica Inc, Piscataway, NJ); (2) overdose, including single doses as low as 360 mg; (3) concomitant use of erythromycin; and (4) significant hepatic dysfunction.

It states that terfenadine is contraindicated in patients taking ketoconazole or erythromycin and in patients with significant hepatic dysfunction and that the recommended dose should not be exceeded. And in some cases, severe arrhythmias have been preceded by episodes of syncope. Syncope in patients receiving terfenadine should lead to discontinuation of treatment and full evaluation of potential arrhythmias.

Rare reports of serious cardiovascular adverse events have been received, some involving QT prolongation and torsades de pointes, in apparently normal individuals without identifiable risk factors. There is no conclusive evidence of a causal relationship of these events with terfenadine, and further studies of this are being undertaken.

Physicians are advised to discuss the potential risk of serious cardiovascular events and specific risk factors with patients, and to refrain from prescribing Seldane to patients with these risk factors. The sponsor has been asked to develop a patient leaflet for immediate use and unit-of-use packaging that will include the leaflet.

Astemizole: Health professionals have also been notified about a box warning, dosing recommendation change, and other information added to the astemizole (Hismanal, Janssen Pharmaceutica Inc, Piscataway, NJ) labeling to warn about the potential for serious adverse cardiovascular events in patients exceeding recommended doses of the drug. While the majority of such events have occurred following substantial overdoses, torsades de pointes (arrhythmia) has very rarely occurred at reported doses as low as 20 mg to 30 mg daily. Therefore, the new labeling highlights that *the recommended doses (10 mg daily) should not be exceeded;* a larger dose during the first several days of treatment is no longer recommended as this may suggest to patients that such doses may be used chronically. It is important to stress to patients that they should adhere to the recommended dose and that excessive doses may lead to serious cardiovascular events. Some patients appear to increase the dose of astemizole in an attempt to accelerate the onset of action. Patients should be advised not to do this and not to use astemizole as a PRN (*pro re nata*) product for immediate relief of symptoms.

Syncope in patients receiving astemizole should lead to immediate discontinuation of treatment and appropriate clinical evaluation, including electrocardiographic testing.

Zalcitabine Approved for Use in Combination With Zidovudine for HIV Infection: The FDA has approved zalcitabine, formerly known as dideoxycytidine or ddC, for use in treating human immunodeficiency virus (HIV) infection. The drug product (HIVID, Hoffmann-LaRoche Inc, Nutley, NJ) is indicated for use in combination with zidovudine, known as AZT (Retrovir, formerly Burroughs Wellcome Co, Research Triangle Park, NC), as a treatment option for adult patients with advanced HIV infection ($CD4^+$ cell count $\leq 300/mm^3$ [$\leq 0.30 \times 10^9/L$]) who show signs of clinical or immunological deterioration.

The approved indication is based on limited data from two small studies in which patients treated with combination therapy had a greater $CD4^+$ cell response than those who received zidovudine alone. In both studies all patients were zidovudine-naive. At present, no data are available on the combined use of zalcitabine and zidovudine in patients who have previously used zidovudine monotherapy. The studies were not designed to measure the clinical efficacy of the combination.

Currently there are no data demonstrating enhanced survival, lowered incidence of opportunistic infections, or decreased progression of HIV infection for patients treated with combination therapy, although four studies investigating clinical benefit of the therapy are ongoing. Because zidovudine has been shown to prolong survival and decrease the incidence of infection in patients with advanced HIV disease, zidovudine monotherapy should be considered as initial therapy for adult patients with advanced HIV infection who have evidence of impaired immunity ($CD4^+$ cell count of ≤ 500 mm^3 [$\leq 0.50 \times 10^9/L$]).

The major clinical toxic effects of zalcitabine are peripheral neuropathy and, much less frequently, pancreatitis. Toxic effects previously associated with zidovudine monotherapy are also likely to occur with the combination therapy.

The approval of zalcitabine is the first to occur under the principles and procedures of the FDA's accelerated drug review policy (*JAMA* 1992;267:3262), which also provides for prompt removal of the product from the market if further review determines that it is ineffective.

—by Stuart L. Nightingale, MD
Associate Commissioner
for Health Affairs

Editor's Note: Written inquiries may be directed to the Office of Health Affairs, FDA, Parklawn Building, 5600 Fishers Ln, Rockville, MD 20857.

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20 Little Britain
London EC1A 7DH
GRANDE BRETAGNE

Application Nr.	Ref.	Date
95 943 722.9-2112	05 29847	08.09.00
Applicant: SEPRACOR, INC.		

Provision of a copy of the minutes in accordance with Rule 76(4) EPC

The attached copy of the minutes of the oral proceedings is sent to you in accordance with Rule 76(4) EPC.

EUROPÄISCHES PATENTAMT - EUROPEAN PATENT OFFICE - OFFICE EUROPÉEN DES BREVETS

THORNTON, J
For the Examining Division
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Enclosure(s): Copy of the minutes (Form 2009)

Application No.: 95 943 722.9

Minutes of the oral proceedings before the EXAMINING DIVISION

The proceedings were not public.

Proceedings opened on 26.06.2000 at 10:00 hours

Examining Division:

Chairman: UIBER P J
1st member: HERRERA S H
2nd member: KLING I V

Minute writer: KLING I V

Present as/for the applicant/s:

JUMP Timothy

accompanied by: HUGUES Sian

The identity of the person/s present and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the oral proceedings and the relevant statements of the applicant/s:

The Representative was asked if the set of claims of 29.05.00 was the last request.

He answered that he wished to amend claim 1 by replacing "by administering to said human" with "said medicament to be administered in an amount sufficient to provide ... to a human" in order to take into account the decision T570/92 which concerns the drafting of Swiss claims. The Representative filed 3 Auxiliary requests numbered (1) to (3) (Annex).

The Chairman of the Examining division said that the four sets of claims were allowable under Article 123(2) EPC and Article 84 EPC and that their content was new according to Articles 52 and 54 EPC as already acknowledged in the previous communication.

The question to be discussed was inventive step. The Chairman gave the floor to the Representative for applicants who argued:

Using the problem/solution approach, the closest prior art is D1 which teaches that DCL is an antihistaminic and is active in the treatment of allergic reaction. However there is no information about which kind of allergic reaction and about which kind of mammals could be treated.
The relevant case law is: T923/92, T694/92 and T207/94 where it was decided that a course of action can be obvious to try with a reasonable expectation of success.
Potency and efficacity are not the only issue in pharmacy, the drug must also be safe.
Safety is the main concern for a clinician who is part of the skilled team.

The Representative went on to say that allergic rhinitis is not a life threatening condition, it is not like for instance cancer.
DCL is the active metabolite of loratidine and both compounds are members of a class.
The Representative cited the Goodman and Gillman's, The pharmaceutical basis of therapeutics, 8th Edition, Pergamon Press (Annex). In particular page 585, Table 23-3, which teaches that terfenadine and astemizole are in the same class of piperidine H1 histamine antagonist., on page 587, last sentence of the second full paragraph: other nonsedating H1 antagonists under study include loratidine (a piperidine).
Their position is that the skilled man would consider that DCL is a member of the class of loratidine and there could be a class effect and therefore DCL could be dangerous.
The compounds are of the same structural class (piperidine) and are both nonsedating

H1 antagonists.

The chairman of the Examining division took the floor and said that there are different metabolites even for a class of compounds and that you cannot derive that all members of the class are behaving the same way. The Chairman said that what is described in E7 is not really a normal use of the drug but more an abuse since the boy used the drug for a very long period of time and that the conclusions might not be extrapolated since it concerns only specific one case and not a general study.

The Representative went on and mentioned E1 (page 770 and 772) and E3 and E5 which teach that loratidine gives QTc arrythmia as a side effect (that was known before the priority of the present application). E8 and E3 disclose that concomitant administration of ketoconazole and terfenadine lead to electro-cardiographic QT prolongation.
DCL could probably cause the same sides effects.
Furthermore since 2 drugs are known to have cardiac side effects: terfenadine and loratidine which causes furthermore personality disorders, the skilled man would think that DCL would cause serious side effects so that the skilled man would not have a reasonable expectation of success that DCL would not have such side effects. The skilled man could think that greater potency could be associated with greater risk.

It has been suggested that D2 teaches that DCL is 10 times more potent than loratidine. Actually it is not the case, D2 teaches that loratidine and DCL have an inhibitory effect on antigen-induced histamine release from the cells which have been studied. However, antihistaminic compounds do not work this way, they work by blocking the receptors. See in particular E6 on page 197 and the Goodman and Gillman's reference, on page 582, the paragraph History.

The Representative disputed the presence of a "bonus effect". The Representative did not think that it would be obvious to find out that there are no side effects such as arrythmia by using DCL and he mentioned the decision T2/83.

The first member of the Examining division noted that the disease - allergic rhinitis - is not a fatal disease. The compounds cited in the Warning of the FDA (E3) should have been withdrawn by the time of E3.

The representative argued that a drug is not just taken out of the market because of a warning of the FDA, it takes a certain time also because there are some commercial considerations.
The chairman of the Examining Division asked the Representative if he had any further comment, what the Representative did not unless the Examining Division had further questions.

The Oral Proceeding were suspended from 11:00 till 11:25

The Chairman informed the Representative that the Examining Division came to the conclusion that the claims of the main request as received during the Oral proceedings on 26.6.00 do not involve an inventive step.

The Auxiliary request (1) complied with the requirements of Article 123(2) EP. The difference resided in the dose ranges.
The representative said that D1 on page 9 discloses a dosage of from 5-100mg/day preferably 10 to 20 mg/day whereas the examples of D1 disclose doses of from 100 or 500 mg per unit dosage which are inconsistent with the relevant parts of the description and claims. He cited the decision T240/88 and said that the Applicants are claiming a much lower range (0.1 to 10 mg/day).

The Applicants had no further comment.

The Oral Proceeding were suspended from 11:35 until 11:40

The Chairman informed the Representative that the Examining Division came to the conclusion that the claims of the auxiliary request (1) as received during the Oral proceedings on 26.6.00 does not involve an inventive step.
The same conclusions apply to the auxiliary request (2).
The same conclusions apply to the auxiliary request (3).

The Application is refused since none of the requests comprises claims which involve an inventive step.

- After deliberation of the examining division, the chairman announced the following **decision**:

"The European patent application is refused."

Regarding the reasons for the decision, the chairman referred to:

Article 97(1) EPC: the application does not meet the requirements of Article/s 52(1) and 56 EPC.

The party/parties was/were informed that the minutes of the oral proceedings and a written decision (including an indication of the possibility of appeal) will be notified to him/them as soon as possible.

The chairman **closed the proceedings** on 26.06.2000 at 11:50 hours.

signed:

UIBER P J

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Chairman

signed:

KLING I V

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Minute writer

Enclosure(s):
Goodman and Gillman's, The pharmaceutical basis of Therapeutics, 8th
main request, auxilairy requests (1), (2) and (3)

Annex I

CLAIMS

1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in treating allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount sufficient to provide a therapeutically effective amount of DCL or pharmaceutically acceptable salt thereof to a human.

2. A use as claimed in claim 1, wherein the medicament further comprises a pharmaceutically acceptable carrier.

3. A use as claimed in either of the preceding claims, wherein said adverse side effect is cardiac arrhythmia or tumour promotion.

4. A use as claimed in any of the preceding claims, wherein said human has a higher than normal propensity for, or instance of, cancer.

5. A use as claimed in any of the preceding claims, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

6. A use as claimed in any of the preceding claims, wherein the amount of DCL administered is from about 0.1mg to less than about 10mg per day.

7. A use as claimed in claim 6, wherein the amount of DCL administered is from about 0.1mg to about 5mg per day.

Annex 2

Auxiliary request (1)

CLAIMS

1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in a treatment of allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount sufficient to provide from 0.1mg to less than 10mg per day of DCL or pharmaceutically acceptable salt thereof to a human.

2. A use as claimed in claim 1, wherein the medicament further comprises a pharmaceutically acceptable carrier.

3. A use as claimed in either of the preceding claims, wherein said adverse side effect is cardiac arrhythmia or tumour promotion.

4. A use as claimed in any of the preceding claims, wherein said human has a higher than normal propensity for, or instance of, cancer.

5. A use as claimed in any of the preceding claims, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

6. A use as claimed in any of the preceeding claims, wherein the amount of DCL administered is from 0.1mg to 5mg per day.

Annex 3

Auxiliary request (2)

CLAIMS

1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in a treatment of allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount sufficient to provide from 0.1mg to 5mg per day of DCL or pharmaceutically acceptable salt thereof to a human.

2. A use as claimed in claim 1, wherein the medicament further comprises a pharmaceutically acceptable carrier.

3. A use as claimed in either of the preceding claims, wherein said adverse side effect is cardiac arrhythmia or tumour promotion.

4. A use as claimed in any of the preceding claims, wherein said human has a higher than normal propensity for, or instance of, cancer.

5. A use as claimed in any of the preceding claims, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

Annex 4

Auxiliary request (3)

CLAIMS

1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in a treatment of allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount sufficient to provide from 0.2mg to 1mg per day of DCL or pharmaceutically acceptable salt thereof to a human.

2. A use as claimed in claim 1, wherein the medicament further comprises a pharmaceutically acceptable carrier.

3. A use as claimed in either of the preceding claims, wherein said adverse side effect is cardiac arrhythmia or tumour promotion.

4. A use as claimed in any of the preceding claims, wherein said human has a higher than normal propensity for, or instance of, cancer.

5. A use as claimed in any of the preceding claims, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.